STAT

Lavishly funded Moderna hits safety problems in bold bid to revolutionize medicine

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Aram Boghosian for STAT

SAN FRANCISCO — Moderna Therapeutics, the most highly valued private company in biotech, has run into troubling safety problems with its most ambitious therapy, STAT has learned — and is now banking on a mysterious new technology to keep afloat its brash promise of reinventing modern medicine.

Exactly one year ago, Moderna CEO Stéphane Bancel talked

up his company's "unbelievable" future before a standing-room-only crowd at the annual J.P. Morgan Healthcare Conference here. He promised that Moderna's treatment for a rare and debilitating disease known as Crigler-Najjar syndrome, developed alongside biotech giant Alexion Pharmaceuticals, would enter human trials in 2016.

It was to be the first therapy using audacious new technology that Bancel promised would yield dozens of drugs in the coming decade.

But the Crigler-Najjar treatment has been indefinitely delayed, an Alexion spokeswoman told STAT. It never proved safe enough to test in humans, according to several former Moderna employees and collaborators who worked closely on the project. Unable to press forward with that technology, Moderna has had to focus instead on developing a handful of vaccines, turning to a less lucrative field that might not justify the company's nearly $5 billion valuation.

"It's all vaccines right now, and vaccines are a loss-leader," said one former Moderna manager. "Moderna right now is a multibillion-dollar vaccines company, and I don't see how that holds up."

Bancel made no mention of the Crigler-Najjar drug when he spoke Monday before a similarly packed room at this year's J.P. Morgan conference.

His presentation instead focused on four vaccines that the company is moving through the first phase of clinical trials: two target strains of influenza, a third is for Zika virus, and the fourth remains a secret. Bancel clicked through graphs of

data from animal studies before hurrying on to tout Moderna's balance sheet and discuss the company's cancer vaccines, slated for clinical testing later this year.

When STAT asked Bancel after the presentation about Crigler-Najjar, he deferred to Alexion.

In need of a Hail Mary

Founded in 2012, Moderna reached unicorn status — a $1 billion valuation — in just two years, faster than Uber, Dropbox, and Lyft, according to CB Insights[5]. The company's premise: Using custom-built strands of messenger RNA, known as mRNA, it aims to turn the body's cells into ad hoc drug factories, compelling them to produce the proteins needed to treat a wide variety of diseases.

But mRNA is a tricky technology. Several major pharmaceutical companies have tried and abandoned the idea, struggling to get mRNA into cells without triggering nasty side effects.

Bancel has repeatedly promised that Moderna's new therapies will change the world, but the company has refused to publish any data on its mRNA vehicles, sparking skepticism from some scientists and a chiding from the editors of Nature[6].

The indefinite delay on the Crigler-Najjar project signals persistent and troubling safety concerns for any mRNA treatment that needs to be delivered in multiple doses, covering almost everything that isn't a vaccine, former employees and collaborators said.

The company did disclose a new technology on Monday that it says will more safely deliver mRNA. It's called V1GL. Last month, Bancel told Forbes[7] about another new technology, N1GL.

But in neither case has the company provided any details. And that lack of specificity has inevitably raised questions.

Three former employees and collaborators close to the process said Moderna was always toiling away on new delivery technologies in hopes of hitting on something safer than what it had. (Even Bancel has acknowledged, in an interview with Forbes, that the delivery method used in Moderna's first vaccines "was not very good.")

Are N1GL and V1GL better? The company has produced no data to answer that question. When STAT asked about new technologies, Bancel referred questions to the company's patent filings.

The three former employees and collaborators said they believe N1GL and V1GL are either very recent discoveries, just in the earliest stages of testing — or else new names slapped on technologies Moderna has owned for years.

"[The technology] would have to be a miraculous, Hail Mary sort of save for them to get to where they need to be on their timelines," one former employee said. "Either [Bancel] is extremely confident that it's going to work, or he's getting kind of jittery that with a lack of progress he needs to put something out there."

Former employees and collaborators who spoke with STAT requested anonymity because they had signed nondisclosure

agreements — which the highly secretive Moderna requires even some job candidates to sign.

A STAT investigation[4] last year found that Bancel had driven away top talent from Moderna with a culture of recrimination and a caustic work environment, including on-the-spot firings for failed experiments.

The company, based in Cambridge, Mass., seems to have repaired its reputation among many rank-and-file employees, winning workplace accolades from Science Magazine and the Boston Globe, but Moderna has lost more than a dozen top scientists and managers in the past four years, despite its vast financial resources.

Moderna - Bancel

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Moderna CEO Stéphane Bancel in the company’s headquarters in Cambridge, Mass.

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A bug in the software

Bancel, a first-time biotech CEO, has dismissed questions about Moderna's potential. He describes mRNA as a simple way to develop treatments for scores of ailments. As he told STAT over the summer, "mRNA is like software: You can just turn the crank and get a lot of products going into development."

It seems clear, however, that the software has run into bugs.

Patients with Crigler-Najjar are missing a key liver enzyme needed to break down bilirubin, a yellowish substance that crops up in the body as old red blood cells break down. Without that enzyme, bilirubin proliferates in the blood, leading to jaundice, muscle degeneration, and even brain damage.

In Moderna's eyes, the one-in-million disease looked like an ideal candidate for mRNA therapy. The company crafted a string of mRNA that would encode for the missing enzyme, believing it had hit upon an excellent starting point to prove technology could be used to treat rare diseases.

But things gradually came apart last year.

Every drug has what's called a therapeutic window, the scientific sweet spot where a treatment is powerful enough to have an effect on a disease but not so strong as to put patients at too much risk. For mRNA, that has proved elusive.

In order to protect mRNA molecules from the body's natural defenses, drug developers must wrap them in a protective

casing. For Moderna, that meant putting its Crigler-Najjar therapy in nanoparticles made of lipids. And for its chemists, those nanoparticles created a daunting challenge: Dose too little, and you don't get enough enzyme to affect the disease; dose too much, and the drug is too toxic for patients.

From the start, Moderna's scientists knew that using mRNA to spur protein production would be a tough task, so they scoured the medical literature for diseases that might be treated with just small amounts of additional protein.

"And that list of diseases is very, very short," said the former employee who described Bancel as needing a Hail Mary.

Crigler-Najjar was the lowest-hanging fruit.

Yet Moderna could not make its therapy work, former employees and collaborators said. The safe dose was too weak, and repeat injections of a dose strong enough to be effective had troubling effects on the liver in animal studies.

The drug, ALXN1540, has since been delayed, as Moderna works on "new and better formulations" that might later reach human trials, Alexion said in an emailed statement.

A huge valuation but a modest pipeline

The failure in its first and most advanced therapy casts doubt on Moderna's other goals for the rare disease space.

It also calls into question Moderna's valuation, pegged at $4.7 billion by Pitchbook. The company has raised nearly $2 billion in cash from investors and partners. But it has done so by promising a revolutionary technology safe enough to deliver

repeated doses of mRNA.

The drugs it is pushing along now, by contrast, are more modest, relying on single administrations of mRNA. Beyond the four vaccines, it has one early-stage clinical trial targeting cardiac disease, launched just last month by partner AstraZeneca. The treatment involves a one-time dose and doesn't use the tricky nanoparticle casing.

Vaccines are not nearly as lucrative as the rare disease space that Moderna hoped to dominate. The market is also much more crowded; at least seven Zika vaccines[12], for instance, are either in clinical testing or are expected to enter testing by next fall.

Moderna has about $1.3 billion in cash on hand, according to Bancel. But with plans to spend more than $300 million a year investing in its technology, it will need to raise more money eventually. The most logical step would be to go public, and last year Moderna reorganized its business to prepare for an initial public offering.

But at its current valuation, Moderna's IPO would be the biggest in biotech history, leaving some investors scratching their heads as to how the company's vaccine-heavy pipeline could justify such a number. If Moderna chooses to stay private, it's unclear whether it can raise more cash without resorting to a dreaded down round, in which new shares are sold at a price below the last ones.

Until Moderna demonstrates that its technology can safely treat a disease, those questions will be tough to answer.

"My friends ask if they are like Theranos, and I say no; I think

it's a real idea," one former Moderna collaborator said. "The question is how well does it work."

Bancel isn't providing the data that could answer that. But he projects unbounded confidence.

"I'm sure that five years from now we'll look at 2017 as the inflection point that Moderna went for a liftoff," he said at Monday's presentation. "We have a chance to transform medicine, and we won't quit until we are done and we have impacted patients."

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